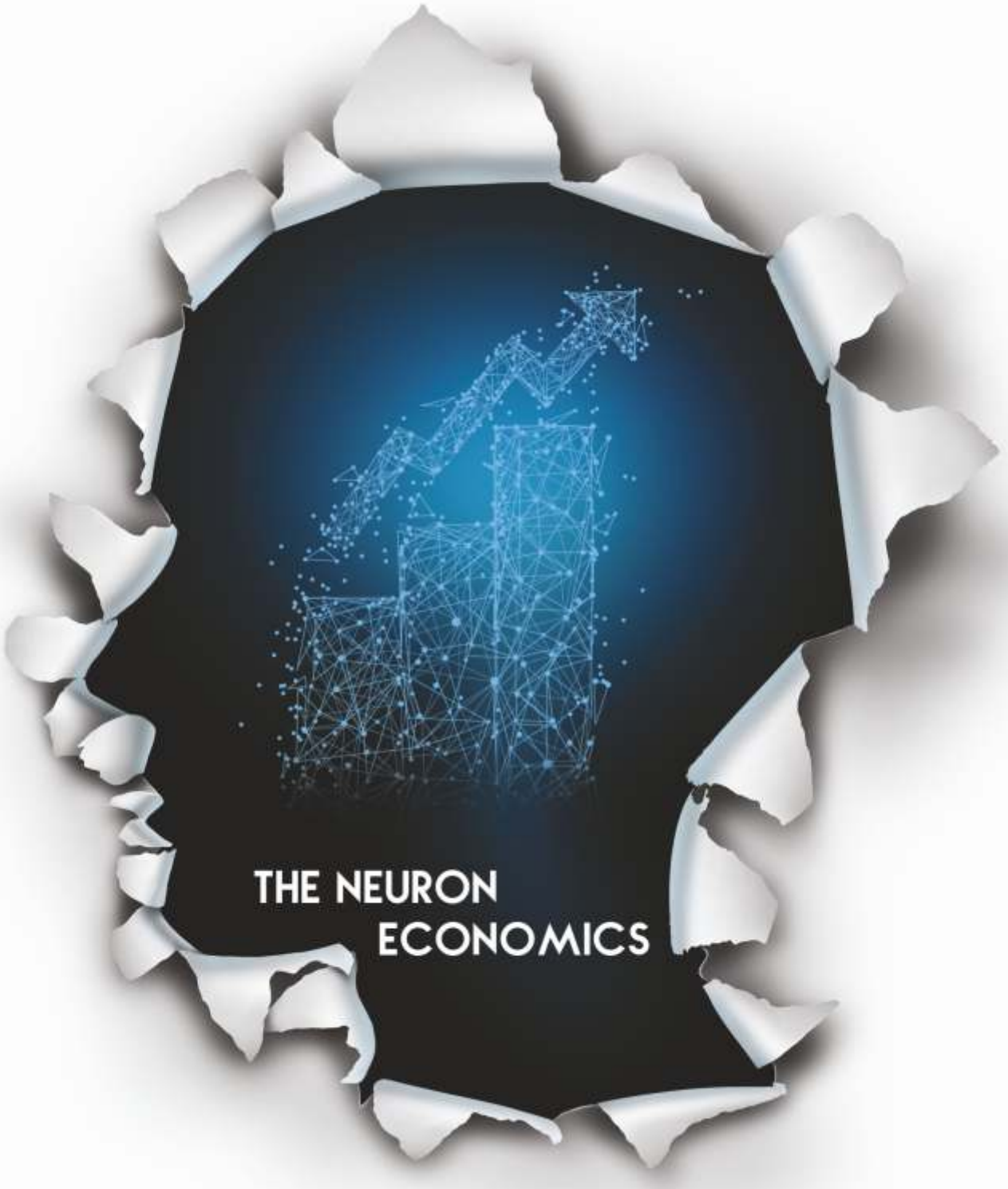


NEURONOMIC

Lactoferrin 100 mg and Disodium Guanosine 5-Monophosphate 10 mg Tablets

Breakthrough Approach | Novel Solution | Patent Applied

IRON – A DOUBLE EDGED SWORD

THE GOOD:

Iron plays a fundamental role in maintaining several biological functions in all living organisms. A few Neurochemical Effects of Iron could be elucidated as follows:

A. Neurotransmitter Signalling:

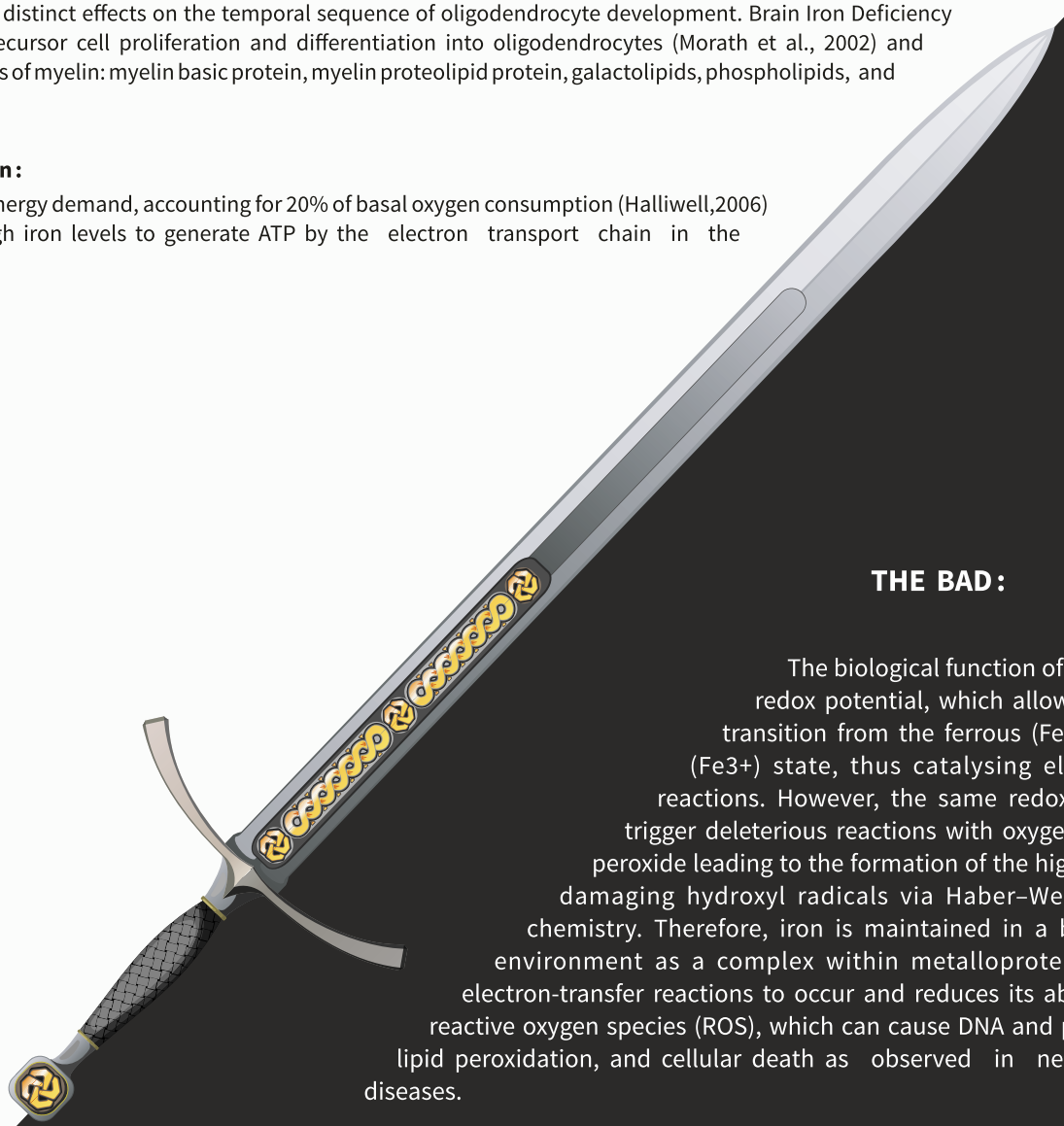
Iron affects synthesis and signalling of the neurotransmitters dopamine, noradrenalin, adrenaline and 5-hydroxytryptamine, which are involved in emotion, attention, reward, movement and various other functions. These neurotransmitters are synthesized by a number of iron-dependent enzymes including phenylalanine hydroxylase (Gottschalletal.,1982), tyrosine hydroxylase (Ramsey et al.,1996), and tryptophan hydroxylase.

B. Myelination:

Iron, has marked, but distinct effects on the temporal sequence of oligodendrocyte development. Brain Iron Deficiency restricts both glia precursor cell proliferation and differentiation into oligodendrocytes (Morath et al., 2002) and decreases components of myelin: myelin basic protein, myelin proteolipid protein, galactolipids, phospholipids, and cholesterol.

C. Energy Production:

The brain has a high energy demand, accounting for 20% of basal oxygen consumption (Halliwell,2006) and thus requires high iron levels to generate ATP by the electron transport chain in the mitochondria.



THE BAD:

The biological function of iron relies on its redox potential, which allows the reversible transition from the ferrous (Fe2+) to the ferric (Fe3+) state, thus catalysing electron-transfer reactions. However, the same redox chemistry can trigger deleterious reactions with oxygen and hydrogen peroxide leading to the formation of the highly reactive and damaging hydroxyl radicals via Haber–Weiss and Fenton chemistry. Therefore, iron is maintained in a bound and safe environment as a complex within metalloproteins that allows electron-transfer reactions to occur and reduces its ability to produce reactive oxygen species (ROS), which can cause DNA and protein damage, lipid peroxidation, and cellular death as observed in neurodegenerative diseases.

OVERVIEW:

Iron plays a crucial role in maintaining normal physiological functions in the brain through its participation in many cellular functions such as mitochondrial respiration, myelin synthesis, and neurotransmitter synthesis and metabolism. Iron distribution within the brain is heterogeneous and the highest concentrations are found in the substantia nigra (SN) pars compacta and basal ganglia.

MECHANISM:

First step in iron transport into the brain is mediated by transferrin uptake and endocytosis through the brain capillary endothelial cells (BCECs) at the blood–brain barrier (BBB). However, subsequent steps of iron release at the abluminal side of the BCECs into the brain interstitium are highly debated and two main hypotheses are:

A. Transcytosis Model – proposes that transferrin is transported into endosomes across the BCECs cytosol and is directly released into the brain.

B. The Receptor mediated Transferrin Endocytosis Model – proposes that iron is released from endosomes in BCECs cytosol via DMT1 and exported into the brain interstitium through ferroportin.

UPTAKE AND REGULATION:

Iron can be stored in ferritin or exported from astrocytes via ferroportin (Fpn) and a physically associated ceruloplasmin (CP). The ferrous iron presented by ferroportin is catalytically oxidized by CP and inserted into extracellular Tf, which is secreted from the choroid plexus. Transferrin is the major iron transport protein of the brain, which is taken up by neurons through TfR1-meditaed endocytosis and internalization in endosomes. Upon acidification in endosomes, iron is released from Tf, reduced to the ferrous form and exported into the cytosol by DMT1. Thus, contributing to the labile iron pool (LIP) of neurons. Iron export from neurons is carried out by Fpn and circulating CP and requires Fpn stabilization by amyloid precursor protein (APP), which is transported to the membrane by the microtubule-associated protein tau.

DYSREGULATION IN NEURODEGENERATIVE DISORDERS:

In neurodegenerative diseases involving iron-mediated toxicity, it has been found that either there may be a failure of iron transport or failure of storage mechanisms. Presence of high levels of non-transferrin-bound iron (NTBI) may also be responsible for iron toxicity over and above the two reasons. Various studies have confirmed that increased iron levels were associated with increased expression of iron importer divalent metal transporter 1 (DMT1) and decreased expression of iron exporter ferroportin1 (FPN1) in PD. The activation of iron regulatory proteins (IRPes) such as Hepcidin was responsible for this abnormal expression of iron transporters. Increased iron and DMT1 expression were also observed in post-mortem AD patients. This indicated that abnormal expression of iron transporters caused iron accumulation and enhanced iron-induced neurotoxicity in AD and PD.

HALLMARK FEATURES:

1. Elevated Ferritin
2. Reduced Expression of Tf
3. Elevated Hepcidin
4. Iron Accumulation in Neurons

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DESCRIPTION:

NEURONOMIC, a patent applied product, is a new approach to manage Neuro Degenerative Disorders by achieving Iron Homeostasis. The present therapies mainly serve as a band-aid therapy, rather than working on the major cause of such NDD which is Dys-Regulation of Iron Homeostasis. NEURONOMIC works to maintain Iron Homeostasis at Neuronal Level and hence help in NDD.

INDICATION:

NEURONOMIC is indicated for the management of Neurodegenerative disease which occurs due to disturbances in Iron Homeostasis.

MECHANISM OF ACTION:

A. Neuronomic - Regulates Hepcidin Ferroportin Axis:

NEURONOMIC, the cationic iron-binding glycoprotein, able to chelate at high affinity (KD w10/20 M) two ferric ions per molecule has been demonstrated to reduce both IL-6 levels and independently reduce Hepicidin gene expression – the two important aspects that are responsible for Iron movement in and out of the cells.

B. NEURONOMIC- Downregulates Inflammation:

Microglia activation-mediated inflammatory processes indeed lead to a vicious circle between inflammatory reaction and neuron damage, and this aggravates the symptoms of PD. In addition, studies found that iron overload could activate microglia and astrocytes and promote the release inflammatory factor and neurotrophic factors, which were involved in the regulation of iron metabolism of DA neurons. Similar is the case in other NDD. **NEURONOMIC** because of its anti-inflammatory properties has also been demonstrated to downregulate the over-expression of macrophages resulting into reduced inflammation which in turn reduces IL-6 levels and upregulates ferroportin expression.

C. NEURONOMIC – antagonize the MPP+ induced Neurotoxicity under the condition of iron overload:

In the brain, Lactoferrin is produced by activated microglia. Immuno -histochemical studies of PD patients have revealed an increase of LfR on SNpc neurons and microvessels possibly as a counter mechanism to combat the iron overload. In VM neurons, both apo-Lf and holo-Lf exerted their neuroprotective effects against 1-methyl-4-phenylpyridine (MPPC) by protecting mitochondria, increasing the expression of copper and zinc-containing superoxide dismutase (Cu/Zn-SOD) and B-cell lymphoma-2 (Bcl-2). This indicated that Lf protected dopaminergic neurons from the neurotoxin.

D. NEURONOMIC – helps in M1 to M2 phenotypic transition of Macrophages:

Microglia activation lead to a vicious circle between inflammatory reaction and neuron damage since activated microglia could also participate in neuroprotection. This “double-edged sword” effect of microglia might depend on different activation states of microglia response to different types of stimuli in normal and disease conditions. It is now recognized that there exist two different activation states of microglia. One is classical activation (M1 phenotype), which contributed to the inflammatory response to produce inflammatory cytokines. This is necessary for antigen presentation to kill intracellular pathogens. However, constant production of inflammatory cytokines could induce cell death in disease conditions. The other state is alternative activation (M2 phenotype), which had an anti-inflammatory phenotype responsible for repair and debris clearance. The proper transition from the M1 to M2 phenotype might be critical for microglia to efficiently end the inflammatory response. However, in PD conditions, persistent released inflammatory cytokines by microglia in the SN usually overshadow the beneficial molecules. It has been hypothesized that lack of M2 phenotype might be an important mechanism involved in neurodegeneration.

DOSAGE & ADMINISTRATION:

2 Tablets a day or as suggested by Healthcare Professional.

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